Lifestyle intervention in obese Chinese adolescents with nonalcoholic fatty liver disease: A randomized controlled study (11122981)

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Background

- Nonalcoholic fatty liver disease (NAFLD) is the most common cause of liver disease in obese children worldwide
- Higher prevalence among obese children (77% [D Chan et al, 2004])
- NAFLD is a growing problem along with the epidemic of obesity in Hong Kong (20% of primary school student are obese in 2015, FHS)
In our previous 2004 report

- NAFLD was common among cohort of obese children referred for medical assessment
  - simple steatosis 77%
  - presumed NASH (hepatic steatosis + raised ALT) 24%
The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD)

Elena Buzzetti, Massimo Pinzani, Emmanuel A. Tsochatzis

Metabolism, Volume 65, Issue 8, 2016, 1038–1048

http://dx.doi.org/10.1016/j.metabol.2015.12.012
Community-based lifestyle modification programme for non-alcoholic fatty liver disease: A randomized controlled trial


Journal of Hepatology
Volume 59, Issue 3, Pages 536-542 (September 2013)
DOI: 10.1016/j.jhep.2013.04.013
Proportion of patients with resolved NAFLD

- Intervention: 64%
- Control: 20%

$P < 0.0001$
Nobili V et al. in 2008 recruited

- 53 children aged 5.7 to 18.8 years
- with mean BMIs of 24.9 to 26.8 and histological NAFLD.
- They were followed for 24 months with a monthly dietary lifestyle modification programme (low caloric diet and regular aerobic exercise) and
- supervised by a multidisciplinary team including dieticians, hepatologists, endocrinologists, psychologists, and cardiologists.
- On average, there was 4 to 6 kg drop in body weight and a significant improvement in histological findings of NAFLD over the 24 months of intervention.

Sustainability
Hypothesis
• Intrahepatic fat content will be decreased after lifestyle modification programme (LMP)

Aim
• To determine the efficacy of LMP in reducing NAFLD in obese adolescents

Primary outcome
• To determine the degree of change of intrahepatic triglyceride content of NAFLD after intervention

Secondary outcome
• To determine the effect of LMP on the obesity by assessing biochemically and by anthropometric measurements
Method

• Randomized controlled trial

• Inclusion
  □ Aged 14-18 post pubertal
  □ Primary obesity
  □ BMI >95th centile
  □ MRS confirmed NAFLD

• Exclusion criteria
  □ Any chronic liver disease, either clinical or biochemical
  □ Alcohol consumption
  □ BMI < 95th centile
  □ Using steatogenic and/or antidiabetic drugs
Diagnosis

• Gold Standard: liver biopsy
• Non invasive method
  – MRS
  – Diagnosis of NAFLD = intrahepatic triglycerides content $\geq 5\%$
Study flow diagram

Obese adolescents assessed by MRS for eligibility (n=79)

Excluded (n=27): no fatty liver

NAFLD patients randomized (n=52)

Intervention group (n=26) (Intention-to-treat analysis)

Status at week 16:
22 received intervention completely
4 lost to follow up
- poor motivation (n=2)
- tight schedule (n=1)
- study abroad (n=1)

Status at week 68:
20 continued intervention during the maintenance phase
6 lost to follow up
- poor motivation (n=2)
- tight schedule (n=2)
- study abroad (n=1)
- unknown reason (n=1)

Patients allocated to intervention group completed the study (n=20) (Per-protocol analysis)

Control group (n=26) (Intention-to-treat analysis)

Status at week 16:
24 received intervention completely
2 lost to follow-up
- tight schedule (n=2)

Status at week 68:
22 received intervention during the maintenance phase
4 lost to follow up
- tight schedule (n=2)
- study abroad (n=1)
- unknown reason (n=1)

Patients allocated to intervention group completed the study (n=22) (Per-protocol analysis)
Inclusion criteria and randomization

Ax T0

Ax:
- MRS
- Anthropometric measurements
- Biochemical measurements

Obese adolescents assessed by MRS for eligibility (n=79)

Excluded (n=27): no fatty liver

NAFLD patients randomized (n=52)

Intervention group (n=26) (Intention-to-treat analysis)

Control group (n=26) (Intention-to-treat analysis)
<table>
<thead>
<tr>
<th>Variables</th>
<th>Intervention group (n=26)</th>
<th>Control group (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>15.3 (3.4)</td>
<td>13.8 (5.3)</td>
</tr>
<tr>
<td>Boys, n (%)</td>
<td>16 (61.5)</td>
<td>18 (69.2)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>91.1 (9.8)</td>
<td>91.1 (8.0)</td>
</tr>
<tr>
<td>Boys</td>
<td>93.7 (7.7)</td>
<td>91.4 (8.2)</td>
</tr>
<tr>
<td>Girls</td>
<td>87.0 (11.6)</td>
<td>90.3 (7.8)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.59 (3.28)</td>
<td>32.12 (3.12)</td>
</tr>
<tr>
<td>Boys</td>
<td>32.26 (3.11)</td>
<td>31.23 (2.92)</td>
</tr>
<tr>
<td>Girls</td>
<td>33.14 (3.63)</td>
<td>34.12 (2.75)</td>
</tr>
<tr>
<td>BMI z-score</td>
<td>2.32 (0.38)</td>
<td>2.29 (0.37)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>103.9 (9.7)</td>
<td>103.6 (7.8)</td>
</tr>
<tr>
<td>Boys</td>
<td>106.0 (9.8)</td>
<td>103.1 (8.2)</td>
</tr>
<tr>
<td>Girls</td>
<td>100.5 (8.8)</td>
<td>104.7 (7.1)</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>41.1 (8.5)</td>
<td>39.0 (9.1)</td>
</tr>
<tr>
<td>Boys</td>
<td>38.4 (7.4)</td>
<td>34.2 (5.5)</td>
</tr>
<tr>
<td>Girls</td>
<td>45.5 (8.7)</td>
<td>49.8 (5.3)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>127 (19)</td>
<td>129 (14)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>71 (13)</td>
<td>71 (9)</td>
</tr>
<tr>
<td>Physical activity level (0-10)</td>
<td>4.8 (2.3)</td>
<td>6.2 (2.1)</td>
</tr>
</tbody>
</table>

Values are mean (SD) or numbers (percentages).
<table>
<thead>
<tr>
<th>Variables</th>
<th>Intervention group (n=26)</th>
<th>Control group (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (IU/L)</td>
<td>22.0 (9.5)</td>
<td>23.2 (9.5)</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>37.6 (26.5)</td>
<td>36.9 (23.6)</td>
</tr>
<tr>
<td>AST/ALT ratio</td>
<td>0.68 (0.36)</td>
<td>0.79 (0.22)</td>
</tr>
<tr>
<td>Insulin (mIU/L)</td>
<td>27.4 (16.2)</td>
<td>27.8 (23.2)</td>
</tr>
<tr>
<td>Fasting glucose (mmol/L)</td>
<td>5.0 (0.4)</td>
<td>4.9 (0.5)</td>
</tr>
<tr>
<td>HOMA</td>
<td>6.3 (4.2)</td>
<td>5.3 (3.1)</td>
</tr>
<tr>
<td>QUICKI</td>
<td>0.50 (0.07)</td>
<td>0.52 (0.12)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.1 (0.4)</td>
<td>1.1 (0.4)</td>
</tr>
<tr>
<td>Intra-hepatic triglyceride content (%)</td>
<td>13.1 (10.2)</td>
<td>13.5 (7.8)</td>
</tr>
</tbody>
</table>

Values are mean (SD) or numbers (percentages).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high density lipoprotein; HOMA, homeostasis model assessment; LDL, low density lipoprotein; QUICKI, quantitative insulin-sensitivity check index.

**NO Difference in all parameters between Intervention and Control**
PHASE I (16 weeks)

Interventional group LMP
Weekly FU by dietitian every 16 weeks

Routine regular FU by Paediatrician every 16 weeks
Intervention - LMP

- 16 weeks LMP
  - An evidence based method developed by the Center for Nutritional Studies
  - Based on motivational interviewing and behavioural modification
- Dietary advice based on American Dietetic Association
  - Emphasis on fruit and vegetables
  - Low fat and low glycaemic index and low caloric food
- Booklet given
- Empower clients themselves on food selection and lifestyle modification
- Psychosocial support
- Logbook 7 days dietary record before each visit
What is lifestyle modification therapy on weight management?

It is a therapeutic application of behavior shaping through operant conditioning. The key components are:

• baseline measurement
• goal-setting
• small, manageable and achievable steps (achievement serves as its own reinforcer and is likely to promote further attempts)
• reinforcement (involves notions of reward and punishment, it then ceases to be purely behavioral but invokes a range of cognitive, affective and social influences to do with motivation and compliance)
Common Strategies used in lifestyle modifications

1. Reinforcements
2. Motivation
3. Health and nutrition education
4. Empowerment
Dietitian

First Ax (1 hour)

Weeky FU (20 mins)

Physical instruction

Pre-intervention Ax

Technique

Compliance (Attendance) rate 81%
Primary Outcome: Intra-hepatic Triglyceride Content (%)

- **Intervention group**
  - Decreased 4.02%
  - Statistically significant decreased when compared with baseline
  - $P = 0.001^{\wedge\wedge}$

- **Control Group**
  - Decreased 0.96%
  - Insignificant

- **Intergroup comparison**
  - $P = 0.029^*$
Post T1 Anthropometric Measurements

Inter-group comparison

*** p<=0.001
** p<=0.01
* p<=0.05

^ P<0.05 (Comparison with baseline)
Post T1 Biochemical Measurements

- **AST/ALT ratio**
- **Fasting Glucose**
- **HOMA**

- [Bar chart showing measurements for I at T1 and C at T1]
PHASE II: MAINTENANCE PHASE FOR 52 WEEKS

Bimonthly dietitian sessions

Conventional consultations
52 weeks
Bimonthly dietary advice by dietitian

Ax T1

Status at week 68:
20 continued intervention during the maintenance phase

Ax T2

Status at week 68:
22 received intervention during the maintenance phase

52 week
Every 16 weeks Follow up
Paed Consultation
Post T2 Anthropometric Measurements

Inter-group comparison

*** p<=0.001
** p<=0.01
* p<=0.05

^ P<0.05 (Comparison with baseline)
At T2, No statistical difference
Comparisons of energy and selected nutrient intakes between the LMP group and control group in baseline, week-16 and week-68

<table>
<thead>
<tr>
<th></th>
<th>LMP group (n=26)</th>
<th>Control group (n=26)</th>
<th>P Value(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Energy, Kcal</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>1769.9 (516.1)</td>
<td>1642.1 (388.5)</td>
<td>0.516</td>
</tr>
<tr>
<td>week-16</td>
<td>1463.0 (517.3)</td>
<td>1478.2 (408.9)</td>
<td>0.578</td>
</tr>
<tr>
<td>week-68</td>
<td>1787.2 (537.2)</td>
<td>1575.7 (453.3)</td>
<td>0.180</td>
</tr>
<tr>
<td><strong>Carbohydrate, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>46.5 (5.7)</td>
<td>46.9 (6.8)</td>
<td>0.795</td>
</tr>
<tr>
<td>week-16</td>
<td>47.4 (6.2)</td>
<td>46.2 (7.1)</td>
<td>0.520</td>
</tr>
<tr>
<td>week-68</td>
<td>47.4 (6.2)</td>
<td>46.0 (9.9)</td>
<td>0.563</td>
</tr>
<tr>
<td><strong>Fat, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>36.2 (4.5)</td>
<td>34.5 (5.8)</td>
<td>0.247</td>
</tr>
<tr>
<td>week-16</td>
<td>31.6 (6.5)</td>
<td>35.6 (5.3)</td>
<td>0.019</td>
</tr>
<tr>
<td>week-68</td>
<td>34.0 (5.7)</td>
<td>35.2 (7.7)</td>
<td>0.556</td>
</tr>
<tr>
<td><strong>Sat Fat, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.3 (2.1)</td>
<td>8.1 (1.7)</td>
<td>0.660</td>
</tr>
<tr>
<td>week-16</td>
<td>7.3 (2.0)</td>
<td>8.5 (2.1)</td>
<td>0.044</td>
</tr>
<tr>
<td>week-68</td>
<td>8.3 (1.8)</td>
<td>9.3 (2.1)</td>
<td>0.088</td>
</tr>
<tr>
<td><strong>Protein, %</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>17.2 (3.5)</td>
<td>18.5 (2.8)</td>
<td>0.151</td>
</tr>
<tr>
<td>week-16</td>
<td>20.6 (3.1)</td>
<td>18.2 (3.2)</td>
<td>0.010</td>
</tr>
<tr>
<td>week-68</td>
<td>18.4 (2.3)</td>
<td>19.0 (4.6)</td>
<td>0.614</td>
</tr>
<tr>
<td><strong>Fiber (g/1000 kcal)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>5.5 (3.0)</td>
<td>5.6 (2.7)</td>
<td>0.847</td>
</tr>
<tr>
<td>week-16</td>
<td>6.6 (3.4)</td>
<td>6.2 (2.0)</td>
<td>0.586</td>
</tr>
<tr>
<td>week-68</td>
<td>5.2 (2.0)</td>
<td>5.9 (2.2)</td>
<td>0.229</td>
</tr>
</tbody>
</table>

**LMP = Lifestyle modification program**

\(^1\) Mean difference between LMP group and control group at each time point by independent t test

\(^2\) Time effect and group*time interaction effect were examined by linear mixed model
Discussion

• LMP
  – Phase I, significantly improvement in reduction of IHTC, BMI, body fat and insulin resistance
  – Phase II, rebound of most of the parameters
  – Persistent significant improvement of total body fat content
  – NAFLD: IHTC still significantly improved when compared with the baseline

• Convention
  – No significant change in primary and secondary outcome
Discussion

• Improvement of the total body fat and NAFLD presented as IHTC might be related to the reduction of fat content in diet
Proposed enhanced program

- Enhanced the existing LMP will be beneficial
- Extend the weekly LMP program
- Additional component in strengthen the internalization of the lifestyle modification is suggested
Limitation and Discussion

• Limitations
  1. nature of the study did not allow blinding of participants
  2. liver biopsy was not performed, so not possible to evaluate necrosis & inflammation
• However, MRS considered an accurate assessment of IHTC and technicians performing MRS were blind to grouping
Conclusion

• Weekly lifestyle intervention for intensive 16-week period reduced body weight & intra-hepatic triglyceride content in obese Chinese adolescents with NAFLD

• Additional component for internalization of the lifestyle modification is suggested for long term effect
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Thank you